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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/672,266	09/25/2003	Byung Sook Moon	020048-004200US	8805

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EXAMINER	
PANDE, SUCHIRA	
ART UNIT	**PAPER NUMBER**
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/672,266	MOON ET AL.	
	Examiner	Art Unit	
	Suchira Pande	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *04 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) *11,13-44,49 and 54-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 12, 45-48, 50-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. This office action is in response to an amendment filed on December 4, 2006.

Claims 1-62 were previously pending. Applicant amended claims 8 and 50; and has not cancelled the withdrawn claims.

Claims 1-10, 12, 45-48 and 50-53 are currently pending and will be examined.

2. Amendments to the specification address the issue of proper use of trademarks.

3. Applicant's amendment overcame the 112 2nd paragraph rejections of claims 8 and 50.

Hence the objections/rejections relating to the above mentioned objections to specification and 112 2nd paragraph rejections of June 23, 2006 non-final rejection are withdrawn.

4. All other previously presented rejections are maintained for the reasons given below.

Response to Applicant's Arguments

Regarding the 103 rejection of claims 1-8,10, 12, 45-48 and 50, 52-53 using prior art taught by Park et al. in view of Treml et al. Applicant argues that

1. The solution taught by Treml et al. contains carbohydrates as minor components.

2. The w/v ranges taught by Treml et al. does not produce w/w ranges claimed by applicant.

Examiner's response: 1. The section cited by applicant from Treml et al. explicitly states " the high molecular weight polymer (carbohydrate) concentration can be between 5% a to 25 % (weight /volume) of the reagent preparation but is preferably 12.5% to 15%. The second carbohydrate is 5% to 15% (w/v). The percent solids in the reagent sphere are between 10% to 50%. ----**The carbohydrates provide most of the mass in the formulations**" (see col. 5 lines 49-58). Hence Treml et al. clearly teaches carbohydrates as major components.

2. Treml et al. teach teaches beads formed with solutions where carbohydrate % is between 5%-15% (w/v). The resulting beads that are formed from this solution will inherently contain same (w/w) ratio as those claimed by applicant. Examiner has clearly demonstrated the relationship derived between w/v and w/w arrived at by Examiner is accurate (see below).

Applicant argues that there are unexpected results with regard to the improved mannitol concentration. As MPEP 716.01(c) notes

> "The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant."

Also in case of overlapping ranges, where the reference teaches an embodiment in the range, the claim is properly rendered prima facie obvious. See In re Peterson, 65

USPQ2d 1379 (Fed. Cir. 2003) . A *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-8,10, 12, 45-48 and 50, 52-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al. 1999 US Pat. 5,861,251 in view of Treml et al. 1998 US Pat. 5,763,157.

Claims 1 and 45 are being considered together because claim 45 is a product by process claim that shares the same structural components namely lyophilized bead suitable for use in amplification of a nucleic acid comprising a thermally stable enzyme

and mannitol as recited in product of claim 1. The process steps (a-c in claim 45) are not being considered for search of prior art. See MPEP 2113 [R1] PRODUCT-BY-PROCESS CLAIMS ARE NOT LIMITED TO THE MANIPULATIONS OF THE RECITED STEPS, ONLY THE STRUCTURE IMPLIED BY THE STEPS.

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

A) Regarding claims 1, 7, 8, 45, 48 and 50 Park et. al. teach:

a. A lyophilized reagent suitable for use in the amplification of a nucleic acid sequence, (see col. 1, lines 5-10, and col. 3, lines 1-10)

b. said lyophilized reagent comprising: a thermally stable enzyme (see col. 3, lines1-10). Park et. al. teach use of DNA Polymerase as the enzyme used for conducting amplification of nucleic acid using polymerase chain reaction where the enzyme is subjected to repeated cycling at high temperatures up to 94^0C. Hence the DNA polymerase used by them is thermally stable as it successfully performs DNA amplification as shown in examples 1-8 (see col. 3, lines 66-67; col. 4, 5 and 6 lines 1-67 of each).

c. And mannitol (see col. 3, line 27). Park et al. use mannitol as a stabilizer. Mannitol is part of their preferred stabilizers falling in the group of polyols

composed of glycerol, glucose, mannitol, galacitol, glucitol and sorbitol (see col. 3, lines 24-30).

Regarding claim 2, Park et. al. teaches amplification in a reaction mixture having a final volume of 50 μl (see col. 4, lines12-13 and lines 47-52).

Regarding claims 3 and 47, Park et. al. teaches dNTPs (see col.4, line 11) and mixture of ddNTPs and dNTPs (see col. 3, lines 1-10).

B) Regarding claims 1 and 45 Park et. al. do not teach:

d. A lyophilized bead wherein said lyophilized bead has a weight percentage of said mannitol of between about 53% and about 75% (w/w).

C) Regarding claims 1, 5-6, and 45 Treml et. al. teach:

e. A lyophilized bead referred to as biological reagent spheres by Treml et. al. suitable for use in the amplification of a nucleic acid sequence (see col. 3, lines 60-67; col. 4, lines 1-8 & col. 7, lines 23-35).

In case of Treml et. al. these beads are composed of a high molecular weight synthetic carbohydrate polymer and a second carbohydrate. Examples of second carbohydrate used by Treml et. al. includes polyols such as sorbitol. The lyophilized beads with weight percentage of second carbohydrate in the range of 5% to 15% expressed in (w/v) are taught by Treml et. al. (see col. 5, lines 49-52). Treml et. al. does not express the weight percentage of polyol in the beads in (w/w). Using the correspondence between % of mannitol in lyophilized beads described in Table 4 of the specification in w/v and w/w it is clear that 7% w/v of mannitol corresponds to 53.75 % w/w of mannitol in lyophilized beads. Similarly

12.77 % w/v of mannitol would correspond to 75% w/w of mannitol in lyophilized beads. Both these numbers of w/v of mannitol namely 7-13 % are within the weight percentage range (5-15% w/v) for second carbohydrate polyol taught by Treml et. al.

Looking at the diameter of beads formed by using mannitol % expressed in w/v in Table 3 (see sizes of beads for 4.5 – 11% mannitol expressed in w/v in the specification) it is clear that these resulting beads are in the size range taught by Treml et. al. see the rejection for claims 4 and 46 below. This provides a further confirmation that the relationship derived between beads with % of mannitol expressed in w/v to w/w as described above is correct.

Hence lyophilized beads of claims 1, 5 and 6 having weight percentage of between about 53% and about 75% (w/w) as recited in claim 1; weight percentage of lyophilized bead between about 62% and about 75% (w/w) as recited in claim 5; and weight percentage of lyophilized bead between about 68% and about 75% (w/w) as recited in claim 6 are taught by Treml et. al.

Regarding claims 4 and 46, Treml et. al. teaches reagent spheres (lyophilized beads) with diameters of about 2 mm to about 6 mm. Preferably, the reagent sphere has a diameter of about 2.5 mm (see col. 3, lines 63-65). Thus lyophilized bead with an average cross-section of about 1 mm and about 4.5 mm are taught by Treml et. al.

Regarding claims 10 and 52, Treml et. al. teaches reagent spheres where the biological reagents are oligonucleotides, proteins, enzymes, DNA or nucleic acids (see co. 4, lines 7-8). All of these are employed as probes in the art for different purposes.

Regarding claims 12 and 53, Treml et. al. teaches reagent spheres where the biological reagent is selected from at least one of the group consisting of DNA/RNA modifying enzymes, restriction enzymes, nucleotides, oligonucleotides, proteins, enzymes, DNA or nucleic acids (see col. 4, lines 4-8). Different molecules may be used as internal control for different purposes. For example DNA could be used as internal control for amplification reactions, therefore Treml et. al. teaches a bead containing internal control.

As described above Park et. al specifically teach use of mannitol as a preferred polyol to be used for stabilizing lyophilized reagents to be used for nucleic acid amplification.

Hence it would have been obvious to one of ordinary skill in the art at the time of the present invention to use the lyophilized beads of Treml et. al. as the lyophilized reagent of Park et al. for use in nucleic acid amplification. The motivation to use lyophilized beads as described by Treml et. al. as lyophilized reagent useful for amplification of nucleic acid taught by Park et. al. is provided by Treml et. al. who describe the limitations and drawbacks associated with the various methods such as dry-blending, spray drying, freeze drying, fluidized bed drying, and /or cryogenic freezing employed for producing dry biological reagents (see col. 1, lines 32-67; col. 2, lines 1-25; col. 3, lines 1-22). They further go on to describe the advantages of their invention namely "providing a homogenous solution of biological reagent(s), glass forming filler material, and water-wherein the shape of droplets formed on an inert cryogenic surface can be controlled by changing the percent solids of emulsion ----------

providing stable storage of a biological reagent that would otherwise be unstable when alone in an aqueous solution at room temperature and providing stable storage of a plurality of biological reagents that would otherwise react with each other when in an aqueous solution at room temperature" (see col.4, lines 51-67 and col. 5, lines 1-9).

8. Claims 8 and 50, are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al. and Treml et al. as applied to claims 1 and 45 above, and further in view of Kellogg et al. (1994) Biotechniques Vol. 16 (6) 1134-1137.

Regarding claims 8 and 50, Park et. al. and Treml et. al. teach the bead of claim 1 and 45 but they do not teach a component selected from the group consisting of an antibody that inactivates a polymerase and a wax or oil to sequester magnesium.

Regarding claims 8 and 50, Kellogg et al. teach an antibody that inactivates a polymerase (see page 1135, par. 3 where a Taq DNA Polymerase that when coupled to neutralizing TaqStartAntibody™, a monoclonal antibody (MAb) directed against Taq DNA polymerase facilitates "Hot start" PCR is taught)

It would have been prima facie obvious to one of ordinary skill in the art to incorporate the Taq DNA Polymerase coupled to neutralizing TaqStartAntibody™, of Kellogg et al. in the product of Park et. al. and Treml et al. at the time the invention was made. The motivation to combine the product of Kellogg et al. in the product of Park et al. and Treml et al. is provided by Kellogg et al. who state "To address the drawbacks inherent in the above methods, we have generated the TaqStartAntibody™, a monoclonal antibody (MAb) the deactivates Taq DNA polymerase at ambient temperature. Heating a reaction mixture to the denaturation temperature reverses the

deactivation of the polymerase and permits the amplification to proceed in a specific and efficient manner. The results indicate that using the antibody greatly reduces non specific products and enhances yield of the specific product" (see page 1135, par. 3).

9. Claims 9 and 51, are rejected under 35 U.S.C. 103(a) as being unpatentable over Park et al. and Treml et al. as applied to claims 1 and 45 above, and further in view of Shively et al. March 2003 BioTechniques vol. 34: (3) pp. 498-504.

Regarding claims 9 and 51, Park et al. teaches a reaction buffer (see col. 2, line 1) that must be part of the reaction mixture before amplification of nucleic acids can take place by PCR. But neither Park et. al. nor Treml et. al. teaches use of buffer HEPES in DNA amplification.

Shively et al. teaches use of HEPES buffer in amplification reactions used to perform Real –Time PCR assay for quantitative mismatch detection. (see page 498 abstract). They describe an assay suitable for quantitative detection of single-base-pair differences that does not require fluorescently labeled gene specific probes. The method requires use of HEPES buffer at a pH of 6.95 together with Ampli-Taq^{R} DNA polymerase results in a threshold difference between the correct template and the mismatched template of as many as 20 cycles, depending on the mismatch. (see page 498, abstract).

It would have been obvious to one of ordinary skill in the art to incorporate the buffer of Shively et al. in the product of Park et al. and Treml et al. The motivation to combine the buffer of Shively et al. in the product of Park et al. and Treml et al. is provided by Shively et al. who state " the technique we describe allows more accurate

quantification because the buffer we utilize results in greater allele-specific differences in threshold cycles (see page 499, par. 1)" and "It was necessary to use HEPES buffer, pH 6.95, instead of the standard Tris-HCl, pH 8.3, for mismatch discrimination at the level shown in Figure 2". (see page 502, par. 3).

Conclusion

All claims under consideration 1-10, 12, 45-48 and 50-53 are rejected.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suchira Pande whose telephone number is 571-272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER
2/8/07